Synthesis of 4-thiazolidinones derived from bicyclic Δ^2-1,2,4-oxadiazolines with potential biological activity

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Abstract

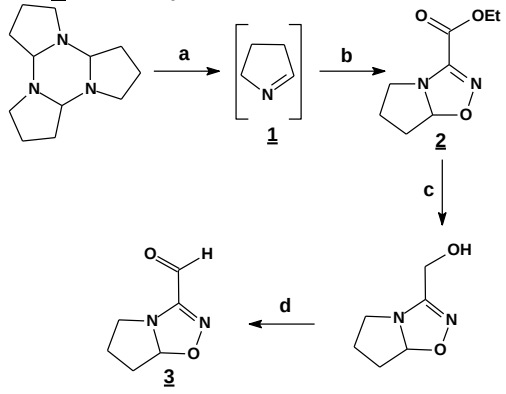
4-thizolidinones have been obtained by cyclization of thiosemicarbazones derived from a Δ^2-1,2,4-oxadiazoline aldehyde.

Introduction

Oxadiazolines have been related as responsible for antinociceptive activity[1]. Our research group has recently synthesized oxadiazolinic compounds that presented similar activity[2]. On the other hand, 4-thiazolidinones have been assayed as angiotensin II inhibitors[3]. In order to obtain molecules containing both pharmacophores, it has been devised a method that aimed the synthesis of the oxadiazolinic aldehyde in C3, thus a condensation with thiosemicarbazides to obtain thiosemicarbazones, and thereafter, cyclization to 4-thiazolidinones.

Results e Discussion

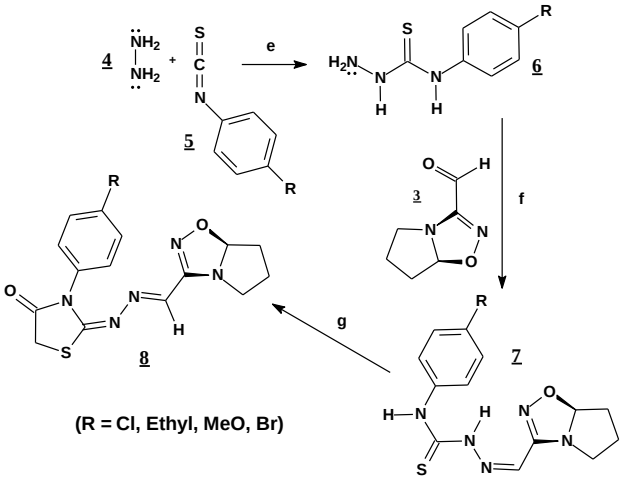
For the purpose of obtaining the oxadizolinic aldehyde **3** (Scheme 1), a 1,3-dipolar cycloaddition (stage b) has been carried out in order to generate an ester **2** in C3, on the oxadiazolinic ring, from Δ^1-pyrroline **1** and ethyl chloro-oxime acetate.



(a) THF, reflux; (b) carboethoxyformonitrile oxide, THF; (c) $NaBH_4$; (d) Swern's oxidation

Scheme 1. Synthesis of the oxadiazolinic aldehyde

Thence, the aldehyde **3** was submitted to condensation reactions (stage f) with thiosemicarbazides **6**, formerly prepared (stage e), by reaction of isothiocyanates **5** and hydrazine **4** (Scheme 2). Subsequently, the thiosemicarbazones **7** underwent reactions with ethyl chloroacetate (stage g), buffered with sodium acetate, to bring forth 4-thiazolidinones **8** in moderate yields.



(e) EtOH, reflux, 4-8h; (f) EtOH, r.t, 1h.; (g) EtOH, ethyl chloroacetate, reflux, 8-24h.

Scheme 2. Synthesis of the 4-thiazolidinones

Conclusions

Besides hydrazones[3] and semicarbazones[4] derived from bicyclic Δ^2-1,2,4-oxadiazolines, published in previous works, it was also possible to obtain thiosemicarbazones and 4-thiazolidinones in reasonable yields (45 – 65%).

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